REMARKS

Claims 1-34 are pending and under examination in this application. New claims 35-43 have been added. Claims 1, 7, 10, 14, 18, 19, 22, 23, 26 and 34 have been amended above. New claims 35-43 have been added. Inadvertent errors in the support cited in Applicants response mailed August 30, 2005, have been corrected below. Similarly, this response is being filed as a Submission under 37 C.F.R. § 1.114, together with the Information Disclosure Statement (IDS) filed on August 30, 2005. Accordingly, Applicants respectfully request this application to be removed from finality and that the IDS be made of record.

Support for the amendments and new claims can be found throughout the application as filed. Specifically, support for the amendments to claims 1, 10 and 34, directed to detecting the release of pyrophosphate (PPi) of simultaneous extensions within a common reaction chamber can be found, for example, at page 12, lines 12-16. Support for the amendments to claims 1, 10, 18 and 34 directed to an attached enzyme at discrete sites on a surface can be found, for example, at page 14, line 34 through page 15, line 24. Support for the amendments to claims 1 and 34 directed to determining sequences for the plurality of target nucleic acids can be found in the preamble of each amended claim. Claim 18 has been amended to recite wherein said array is configured for simultaneous contact of said different capture probes with a common reaction chamber, support for which can be found in the specification for example at page 12, lines 12-16. Claims 22 and 23 have been amended to more properly reflect the antecedent relationships to the base claim. Support for the amendment to claim 26 can be found in the specification, for example, at page 24, line 18 through page 25, line 22. Support for new claims 35, 38 and 43 can be found, for example, at page 14, line 34 through page 15, line 24. Support for new claims 36 and 41 can be found, for example, at page 5, lines 32-36. Support for new claims 37 and 42 can be found, for example, at page 5, lines 36-37. Support for new claims 39 and 40 can be found, for example at page 14, lines 13-19. Accordingly, the amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Applicant would like to thank Examiner Strzelecka for extending a personal interview with Applicant and Applicant's representatives on August 9, 2005. The amendments above and remarks below are believed by Applicant to substantially conform to the subject matter discussed in the interview and result in the Examiner's reconsideration of the rejections.

Rejections Under 35 U.S.C. § 103

Claims 1-4, 6-10, 12-17 and 22-27 stand rejected under 35 U.S.C. § 103 as obvious over Navot et al., United States Patent No. 6,335,165 and Walt et al., United States Patent No. 6,327,410. The Office maintains that there would have been motivation to combine the cited Navot et al. and Walt et al. patents. The Office alleges that Navot et al. teaches pyrosequencing of nucleic acids which may be attached to microbeads in an electrophoresis-free system. Attachment to a solid support provides confinement to the sample. Walt et al. is alleged to describe microbeads with attached nucleic acids randomly distributed on the surface of a fiber optic bundle so as to create a microbead array. The Office further asserts that one skilled in the art would have been motivated to use the microbead array of Walt et al. to detect the microbead reactions of Navot et al. allegedly because fiber optic arrays are inexpensive and allegedly because the synthesis of bioactive agents is the same as DNA sequencing.

The invention is directed to a method of sequencing a plurality of target nucleic acids. The method includes providing an array having a substrate with discrete sites, a population of microspheres having at least first and second subpopulations and an enzyme for generating a pyrophosphate signal attached at the discrete sites. Providing a first hybridization complex containing a first target sequence attached to the first subpopulation. Providing a second hybridization complex containing a second target attached to the second subpopulation. Simultaneously extending the first and second primers, and detecting the release of pyrophosphate (PPi) with the enzyme attached at the discrete sites within a common reaction chamber of the simultaneous extensions to determine the sequence of the plurality of target nucleic acids.

Navot et al. is directed to methods and kits of characterizing a GC rich region of a nucleic acid of interest derived from an individual for diagnostic purposes (see Abstract, column 10, lines 17-19). Navot et al. further describes restricting each sequencing reaction to a separable confinement (see Office Action at page 3, *citing* Navot et al., col 15, lines 1-14). Navot et al. patent does not disclose large scale sequence determination involving a plurality of target nucleic acids. Walt et al. is directed to compositions encompassing a substrate and a population of distributed microspheres. The microspheres can include subpopulations of bioactive agent and

corresponding optical signatures capable of identifying the corresponding bioactive agent (see Summary of the Invention).

Where an invention is contended to be obvious based upon a combination of elements across different references, the Federal Circuit case law "require that there be a suggestion, motivation or teaching to those skilled in the art for such a combination." *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." *Id.* (citing *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1371-72 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (abrogated on other grounds)). Further, obviousness can be rebutted where it is shown that the prior art taught away from the claimed invention. *Iron Grip Barbell, Co.* Case No. 04-1149, slip op. at 7 (citing *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997)).

Applicants respectfully submit that the cited combination of references fail to teach, suggest or motivate those skilled in the art to combine elements of the method of the invention as they are claimed. For example, the cited references fail to provide a teaching, suggestion or motivation for the claimed combination at least because they fail to provide motivation to detect the release of pyrophosphate (PPi) for the simultaneous extension reactions within a common reaction chamber Further, Applicants maintain that the comparison of methods for synthesizing random and spotted arrays at column 4, lines 44-59 of Walt et al. does not provide a motivation to combine the disclosures of Walt et al. and Navot et al. to arrive at the claimed invention because the description is directed to allowing "synthesis of the bioactive agents . . . to be *separated* from their placement on an array" (emphasis added, see col. 4, lines 43-46), whereas the claims include, *inter alia*, extending primers hybridized to an array.

Applicants claim detecting the release of pyrophosphate (PPi) for simultaneous extension reactions in a common reaction chamber. Released pyrophosphate is a diffusible product of the pyrophosphate sequencing reaction. Navot et al. expressly describes that each sequencing reaction should be separated in a confinable compartment in order to detect signals from the

separate reactions. Navot et al. expressly teaches away from detection released pyrophosphate from multiple reactions in a common reaction chamber when Navot et al. state:

> The reaction is typically performed sequentially in a single confinement, wherein in each cycle a different nucleoside triphosphate or analog is added to the confinement and the luminescence monitored. Additional cycles are performed after carefully washing the confinement ensuring that the template and the complementary nucleic acid growing chain are remained confined in the confinement.

Navot et al., col. 13, lines 28-35 (emphasis added).

Accordingly, Navot et al. teaches away from the invention as claimed because Navot et al. teaches confinement of single pyrophosphate reactions. Such a teaching away defeats any motivation to combine the separated pyrosequencing reactions of Navot et al. with the array of Walt et al. to obtain the claimed invention where detection of released pyrophosphate occurs in a common reaction chamber. Absent a teaching, suggestion or motivation to detect the released pyrophosphate as claimed, the cited references cannot render the claimed invention obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 5, 11 and 33 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Balch et al., United States Patent No. 6,083,763. Balch et al. is cited as further disclosing adapter probes.

As set forth above, a lack of motivation exists to combine Navot et al. and Walt et al. to arrive at Applicants' claimed invention. In particular, Navot et al. expressly teaches away from detecting the release of pyrophosphate (PPi) from the simultaneous extension reactions within a common reaction chamber. This deficit is not cured with regard to claims 5, 11 and 33 by further citation of the Balch et al. patent. In addition, nothing in the Balch et al. reference would have provided a motivation to the skilled artisan to combine this reference with Navot et al., *supra*, and Walt et al., *supra*. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Claims 18-21 and 28-30 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Navot et al., *supra*, and Walt et al., *supra*, and further in view of Nyren et al., WO 98/13523. The international patent publication by Nyren et al. is cited as a further secondary reference for allegedly disclosing kits encompassing a sequence primer, a polymerase, a detection enzyme means for identifying pyrophosphate relief, dNTPs or ddNTPs.

The Office Action maintains that both Navot et al. and Nyren at al. describe pyrosequencing and pyrosequencing kits with different sets of reaction components, interpreting these descriptions to be "strong motivation" to combine different reaction components into kits.

Applicants respectfully point out that the kit of claim 18 includes a substrate with a surface having discrete sites and a population of microspheres having capture probes. Any description of a kit having different sets of sequencing reaction components fails to provide a desirability to combine with an array. Claim 18 also includes an enzyme attached at discrete sites and an array configured for simultaneous contact of different capture probed with a common reaction chamber. None of Navot et al., Walt et al. or Nyren et al. teach, suggest or provide motivation to combine these elements as claimed. Absent such a teaching, suggestion or motivation, the invention as claimed is not rendered obvious over the cited references and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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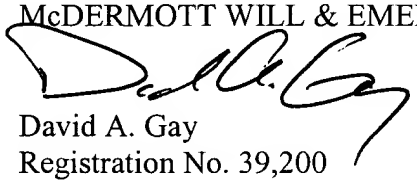

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